Remarks

The Final Office Action dated March 11, 2003 and the Advisory Action dated October 1, 2003 have been carefully reviewed and the foregoing amendments are made in response thereto. In view of these amendments and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

All of the previously pending claims have been cancelled without prejudice or disclaimer. The cancelled claims have been rewritten as claims 37 to 61 to better define the claimed invention. Applicants respectfully submit that no new prohibited matter has been introduced by these amendments. While written description support for the amendments and additional claims can be found throughout the specification and in the original claims, examples of specific support for the additional claims can be found in the specification as set forth in the table below.

Claim	Support in Specification
37	page 7, lines 20-24
38	page 2, lines 29-31
39	page 7, lines 20-22
40	page 18, lines 21-22
41-45	page 3, lines 8-10; page 6, lines 17-22
46	page 8, lines 12-14
47	page 13, lines 17-22
48	page 27, lines 4-17
49	page 14, line 28 to page 16, line 24
50	page 3, lines 11-14
51	page 17, lines 3-12
52-56	page 3, lines 14-16
57	page 13, lines 18-22
58	page 2, lines 29-31
59-60	page 20, lines 14-15
61-63	page 17, lines 22-27

Summary of Final Office Action

1. Claims 25, and 27-29 were restricted for being directed to an invention that is independent or distinct from the invention originally claimed. Claims 30 and 34-36 were restricted as far as they depend from claims 25 and 27-29.

2. Claims 31-33 were rejected under 35 U.S.C. 112 (first paragraph) as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention.

3. Claim 34 was rejected under 35 U.S.C. 112 (first paragraph) as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

4. Claims 24 and 30 were rejected under 35 U.S.C. 102(b) as being anticipated by Sala *et al.* (1994) J. Virol. 68, 5280-5283 and Lukashov *et al.* (1996) SPTREMBL_17 database; Accession No. Q69692.

5. Claim 26 was rejected under 35 U.S.C. 103(a) as being unpatentable over Sala *et al.* (1994) J. Virol. 68, 5280-5283.

6. Claims 35 and 36 were rejected under 35 U.S.C. 103(a) as being unpatentable over Sala *et al.* (1994) J. Virol. 68, 5280-5283 in view of Haynes *et al.* (U.S. Patent 5,019,387).

7. Claims 2 and 23 were found to be allowable.

Remarks

In the advisory action dated October 1, 2003 the Examiner indicated that the amendment filed September 11, 2003 would not be entered on the grounds that the claimed subject matter would require further search and consideration. Applicants respectfully disagree but nonetheless filed a request for continued examination to have this subject matter considered by the Examiner.

Correction of Sequence Listing

Applicants have attached a declaration under 37 C.F.R. 1.132 by Gerald V. Quinnan which sets forth the circumstances in which a sequence error in SEQ ID NO: 1 (HIV envelope protein gp160, R2 strain) in the as-filed specification and sequence listing was discovered. A substitute sequence listing and amendment to Table 3 on page 33 of the specification are attached to correct this error. Applicants respectfully request that the substitute sequence listing and the amendment to the specification be entered.

Response to Second Restriction Requirement

The Office Action withdrew claims 25 and 27 to 29 from consideration as being directed to a non-elected invention. In addition, claims 30 and 34 to 36 as they depend from claims 25 and 27-29 were

considered by the Examiner to be directed to an invention that is independent or distinct from the invention originally claimed. The Office Action indicates that the claims were grouped so that one invention was drawn toward the amino acid sequence comprising SEQ ID NO: 1 and the other invention was drawn toward the amino acid sequence comprising SEQ ID NO: 24. Applicants have cancelled these claims therefore the rejection is moot. Applicants submit that the substitute claims are all drawn to a single invention encompassing an isolated HIV envelope protein or fragment thereof and a method of generating antibodies using this protein or fragment.

Rejections under 35 U.S.C. 112 (first paragraph)

The Office Action rejected claims 31 to 33 under 35 U.S.C. 112 (first paragraph) purportedly because the claims as written contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the Applicants had possession of the claimed invention at the time the application was filed. Without acquiescing to the merits of this rejection, Applicants have canceled claims 31-33, and therefore the rejection is moot.

In addition, the Office Action rejected claim 34 under 35 U.S.C. 112 (first paragraph) purportedly because the claim contains subject matter that was not described in a manner as to enable one skilled in the art to make and/or use the invention. Specifically, the Examiner rejected the claim for being drawn to a vaccine as one of skill in the art would doubt the efficacy of the claimed vaccine. Even though Applicants disagree with this position, this claim has been cancelled without prejudice or disclaimer, therefore the rejection is moot. The substitute claims are drawn toward a composition comprising an isolated HIV-1 envelope protein of the claimed invention and a pharmaceutically acceptable carrier.

Rejections under 35 U.S.C. 102(b)

Claims 24 and 30 were rejected under 35 U.S.C. 102(b) as being anticipated by Sala *et al.* or Lukashov *et al.* The Office Action states that the references disclose an HIV envelope protein fragment that is at least 13 amino acids in length comprising the required amino acid residues in the required position numbers of SEQ ID NO: 1. In addition, the Examiner states that because the protein fragments of Sala *et al.* or Lukashov *et al.* comprise the required structural features specified by the claims, the fragments also inherently possess the ability to produce antibodies against HIV-1 strains *in vitro*. Although Applicants respectfully disagree, these claims have been canceled without prejudice or disclaimer and therefore the rejection is moot. The substitute claims are drawn to an isolated HIV

envelope protein comprising SEQ ID NO:1 or a fragment thereof of at least 37 amino acids. Neither Sala *et al.* nor Lukashov *et al.* disclose an amino acid sequence of at least 37 amino acid residues. Thus, neither reference discloses nor suggests each and every element of the substitute claims.

Rejections under 35 U.S.C. 103(a)

Claim 26 was rejected under 35 U.S.C. 103(a) as being unpatentable over Sala *et al.* or Lukashov *et al.* The Examiner states that while neither reference teaches the entire glycoprotein, the amino acid sequence of the fragment taught by either reference nonetheless renders the claimed HIV envelope protein from which the V3 sequence is derived as obvious. While this claim has been cancelled without prejudice or disclaimer, Applicants still disagree with the position of the Examiner. As the Examiner noted in the Office Action dated June 18, 2002 (Paper 11), "hypervariability of sequences among the different HIV strains is a well recognized concern in the HIV art" (see page 6, lines 14-15). Given this statement, it is not possible that one can assume anything from a partial sequence of an envelope protein with regard to the remainder of the envelope protein sequence.

Claims 35 and 36 were also rejected under 35 U.S.C. 103(a) as being unpatentable over Sala *et al.* or Lukashov *et al.* in view of Haynes *et al.* (US 5,993,819). The Examiner states that the skilled artisan would have been motivated to combine the disclosure of Haynes *et al.* relating to induction of antibodies with HIV proteins, with the disclosure of the envelope sequences of Sala *et al.* to arrive at the claimed invention. Claim 35 and 36 have been canceled without prejudice and disclaimer and therefore the rejection is moot.

Applicants bring to the attention of the Examiner that neither Sala *et al.* nor Lukashov *et al.* disclose an HIV envelope protein meeting the limitations of the substitute claims. In order for one skilled in the art to combine either Sala *et al.* or Lukashov *et al.* with Haynes *et al.* to generate antibodies comprising the limitations of the claimed invention, it would have been necessary for the artisan to know the entire amino acid sequence of SEQ ID NO: 1. At the time of the invention, the complete amino acid sequence of SEQ ID NO: 1 was not known in the art. Thus, there would have been no motivation to modify non-existent teachings with Haynes *et al.* to arrive at the claimed invention. The Office Action has improperly used inherency to fill the gaps in the references because the inherent properties of the claimed envelope protein (*e.g.*, induction of antibodies cross-reactive against multiple strains of HIV-1 *in vitro*), properties first disclosed by Applicants in the present application, were incorrectly considered by the Examiner to support the instant rejection.

It is long and well established that "inherency" and "obviousness" are distinct concepts, which must not to be confused. See *e.g.*, *W.L. Gore & Associates v. Garlock Inc.*, 721 F.2d 1540, 1555 (Fed. Cir. 1983). Appellants submit that the issue is not what may or may not be inherent in the cited references, but rather what is known to the ordinary, skilled artisan from those references. As stated in *In re Newell*, 891 F.2d 899 (Fed. Cir. 1989), "that which may be inherent is not necessarily known ... obviousness cannot be predicated on what is unknown" (Id. at 901); see also *In re Rijckaert*, 9 F.3d 1531, 1535 (Fed. Cir. 1993); *Kloster Speedsteel AB v. Crucible Inc.*, 793 F.2d 1565, 1576 (Fed. Cir. 1986) (holding claims not invalid where defendant failed to show that "inherency would have been obvious to those skilled in the art when invention ... was made").

Applied here, the foregoing authorities make it clear that the inherent and unknown properties of the claimed HIV-1 envelope protein cannot form the basis of an obviousness rejection because the cited references are devoid of any suggestion that the use of the claimed protein to induce production of antibodies cross-reactive against multiple strains of HIV-1.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, she is invited to telephone the undersigned at their convenience.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which my be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **Constructive Petition for Extension of Time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted
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Robert Smyth
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PATENT
Attorney Docket **044508-5001-US**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Gerald Quinnan *et al.***

Application No. **09/762,261** — Group Art Unit: **1648**

Filed: **29 May 2001** — Examiner: **Shanon Foley**

For: **Expression and Characterization of HIV-1 Envelope Protein Associated With a Broadly Reactive Neutralizing Antibody Response**

DECLARATION UNDER 37 C.F.R. 1.132

I, Gerald V. Quinnan, do hereby make the following declaration:

1. I am an inventor in the above-referenced application.

2. I have reviewed the Office Action dated March 11, 2003, in particular the Examiner's comments concerning the protein sequence corresponding to SEQ ID NO: 1 (HIV envelope protein gp 160, R2 strain). I have also reviewed the Sequence Listing filed with the above application on 29 May 2001 and noted an error in this Sequence Listing. Specifically, amino acid 650 which is designated as lysine should be designated as serine.

3. The nucleotide sequence encoding the HIV envelope protein R2 in the region of amino acid 650 was originally sequenced on 21 October 1997 using automated nucleotide sequencing methods. The source of the nucleotide sequence was as disclosed in Quinnan *et al.* (1999) AIDS Res. Hum. Retrovir. 14, 939-949. At that time, amino acid 650 (which corresponds to nucleotides 1950-1952 and is encoded by the codon AAG) was assigned as lysine. The deduced amino acid sequence was included in Provisional Application 60/095,267 (see Table 3) filed on August 4, 1998 to which the instant application claims priority.

4. During subsequent research in my laboratory utilizing this same nucleotide sequence to generate variants of the HIV envelope protein R2, it was determined that the original assignment of amino acid 650 in SEQ ID NO: 1 was incorrectly assigned as lysine and should have been assigned as serine. Upon reviewing the amino acid sequence listed in Table 3 (SEQ ID NO: 1) of the above utility

application on 22 July 2003, I recognized that SEQ ID NO: 1 in this Table had not been updated to correct this error.

5. To investigate this matter further and confirm our finding of 22 July 2003, a sample of the original cDNA encoding the HIV envelope protein R2 was obtained from storage in my laboratory at the Uniformed Services University of the Health Sciences in Bethesda, Maryland. The cDNA was re-sequenced in both directions in this region on 13 August 2003. The repeat nucleotide sequencing confirmed that the correct codon for amino acid 650 is AGC and that the correct amino acid assignment at this position is serine.

6. Based on the above findings, the amino acid sequence of SEQ ID NO: 1 in the as-filed sequence listing and in Table 3 (page 33) of the specification should be corrected to designate amino acid 650 as serine as opposed to lysine.

7. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

9/10/03
Date

Gerald V. Quinnan, ~~Ph.D~~. MD